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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,722	06/27/2001	Alastair David Griffiths Lawson	1300-1-007	4141

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,722	LAWSON ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-38,40 and 41* is/are pending in the application.

4a) Of the above claim(s) *19-33,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Prosecution on this case is HEREBY REOPENED.

2. Applicant's amendment filed 7/25/05 is acknowledged and has been entered.

Claims 34-38 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the instant invention, a nucleic acid sequence encoding a chimeric receptor containing two independent polypeptide chains, one chain comprising a VH extracellular ligand association domain, *i.e.*, an antigen binding region of VH, a spacer domain including from CD8, a transmembrane domain from all or part of human CD4 transmembrane domain and an intracellular domain that is a signaling domain comprised of any naturally occurring polypeptide signaling sequence that is all or part of the human CD4 intracellular signaling domain, the other chain comprising a VL antigen binding region domain, a spacer domain including from CD8, a transmembrane domain that is all or part of human CD4 transmembrane domain and TCR zeta chain signaling domain or a part of said domain, and wherein the chimeric receptor is in association with a carrier that is a viral, liposomal or plasmid vector, a cationic lipid or an antibody, and wherein the two chains of the chimeric receptor do not associate except in the presence of bound ligand. The specification has not enabled the breadth of the claimed invention because the claims encompass *in vivo* or *ex vivo* gene therapy. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed chimeric receptor can be used for the disclosed purpose, except in instances where CTL that are capable on their own of effecting a therapeutic response via adoptive transfer are transduced or transfected *ex vivo* with the said nucleic acid and then adoptively transferred.

The specification discloses no working examples with regards to the use of the instant invention for gene therapy of any type.

The specification discloses that plasmids containing nucleic acid molecule(s) encoding the chimeric receptor may be transfected into Jurkat cells and the resulting transfected Jurkat cells produce IL-2 in the presence of CD33 positive HL60 target cells *in vitro* (especially page 14 at lines 32-36 and pages 15-16). The specification further discloses that for *ex vivo* use, the DNA may be introduced into effector cells removed from the target host, such cells being CTL, TIL, NK, neutrophils, basophils, TH cells, dendritic cells, B cells haematopoietic stem cells, macrophages, or monocytes, *i.e.,* hematopoietic lineage cells (page 9 at lines 6-21). The specification discloses that the DNA may be suitable for *in vivo* administration in the form of a pharmaceutical composition for therapeutic or diagnostic purposes, for treatment of a human or animal subject for such disorders as infectious diseases such as HIV, inflammatory diseases, autoimmunity such as rheumatoid arthritis, osteoarthritis or IBD, cancer, allergic/atopic diseases such as asthma, eczema, congenital diseases such as CF or sickle cell anemia, dermatologic diseases such as psoriasis, neurologic diseases such as MS, transplant rejection or graft vs host disease and metabolic/idiopathic diseases such as diabetes (pages 9-12). The specification discloses that antibody targeted DNA may be used, particularly antibody targeted naked or condensed DNA, and especially antibody targeted liposomes (page 10 at lines 4-6), however, no working examples of antibody targeted DNA are disclosed.

The practice of *in vivo* or *ex vivo* gene therapy constitutes a highly unpredictable art, requiring undue experimentation to enable one skilled in the art to use such an invention. At the time the parent application was filed, successful use of gene therapy was not routinely obtainable by those skilled in the art, nor was there any reasonable expectation of success for any given protocol given the state of the art at the time. Evidentiary reference Orkin *et al* reviewed the infant state of the art of gene therapy at around the time the invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges, 2) no successful gene therapy protocol was known, 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors, 4) the pathophysiology of diseases to be treated were poorly understood, 5) one can not predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as a human, 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints, and 7) gene therapy has been oversold, and the impression that gene therapy is successful is mistaken. The specification does not disclose how one skilled in the art is to overcome any of the problems that have plagued gene therapy.

In addition, references that post date the instant invention by several years indicate that these problems still exist and have not yet been solved.

Evidentiary reference Gardlikk *et al* (Med. Sci. Monit. 2005, 11(4): RA110-121) teach that the main safety problem of gene therapy lies in the secure and efficient delivery of genes into target cells and tissues, that two kinds of vectors, *i.e.*, viral vectors and non-viral vectors such as plasmids and liposomes, have been employed as vehicles for gene transfer, yet none of these types of vectors has been found to be ideal for both safe and efficient gene transfer and stable and sufficient gene expression (especially abstract and paragraph spanning columns 1 and 2 on page RA111). Gardlikk *et al* further teach that injecting naked DNA encoding a therapeutic protein has low efficiency (especially fifth paragraph on page RA111). Gardlikk *et al* conclude that although clinical trials have been started, there are still numerous limitations that must be solved before routine clinical use (especially last paragraph on page RA119).

Evidentiary reference Verma and Weitzman (Ann. Rev. Biochem. 2005, 74: 711-738) teach that vector development remains a seminal concern for improved gene therapy trials, that there are presently no commercially approved gene therapy treatments, and that deaths have resulted from administration of gene therapy vectors (especially abstract, pages 730-732 through the first full paragraph). Verma and Weitzman further teach that that gene therapy has yet to deliver its promised potential, and that it is a future task for virologists to develop efficient and safe vectors that are able to deliver genes of interest to target cells and that assure the proper expression of the transferred genetic material (especially second full paragraph on page 732).

Evidentiary reference Goncalves (BioEssays, 2005, 27: 506-517) teaches serious adverse events such as death resulting from clinical gene therapy trials. Goncalves teaches that further improvements in gene transfer technologies and deeper insights in host-vector interactions are warranted before clinical gene therapy reaches maturity, *i.e.*, knowledge of control over transgene expression and integration and knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity (especially Conclusions section on pages 514-515).

Nor was the technology for successful use of *ex vivo* gene therapy routinely achieved at the time the invention was made (see Kay *et al.* 1997, 94: 12744-12746, especially page 12746; Anderson, Nature, 1998, 392: 25-30, especially page 25, top right column). Attempts at *ex vivo* gene therapy have been generally focused on transfer of transduced hematopoietic stem cells. While lethally irradiated mice can be reconstituted with retroviral vector transduced syngeneic bond marrow such that the cells can provide genetically marked progeny persisting in blood and bone marrow over extended time periods, hematopoietic stem cells from large animals are much more refractory to gene transfer, cell engraftment, and sustained long-term expression coincident with HSC repopulation and expansion (Chu *et al.* J. Mol. Med., 76: 184-192,

1998). Kay reported that the frequency of retrovirally transduced stem cells after transplantation in a human subject is only 0.001% of the endogenous stem cells, too low to result in detectable, stable engraftment (especially pages 12,746, column 1). A retroviral transduction efficiency leading to 0.01%-5% provirus positive circulating cells is too low to expect clinical improvement for the majority of human diseases associated with hematopoietic system (Havenga *et al.*, Stem Cells, 15: 162-179, 1997). Gene transfer into HSCs assessed by in vivo reconstitution experiments in cats, dogs and monkeys have failed to show clinically relevant levels of HSC gene transfer, and including by 1 year post-transplant despite the use of in vivo cytoablation regimens, inclusion of growth factors during transduction or the enrichment of hematopoietic progenitors and HSCs (Chu *et al*, pg 187, bottom left paragraph). In all, Chu *et al* conclude that "currently available HSC gene transfer protocols do not reliably transfer genes into HSCs with long-term repopulating capacity" (especially last paragraph on page 189). Havenga et al arrived at a similar assessment in concluding that "for gene therapy to become a clinically relevant treatment, several problems have to be overcome... include[ing] the identification of human PHSCs and the golden mixture of factors allowing ex vivo PHSC cycling and transduction without losing grafting potential" (especially last paragraph on page 174).

There is insufficient guidance in the specification as to how to use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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